PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

TANAKA, et al.

Application No.: New application

Filed: Concurrently herewith

Attorney Dkt. No.: 107380-00005

For: NEW IMAGING AGENTS, PRECURSORS THEREOF ND METHODS OF MANUFACTURE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

June 4, 2001

Sir:

Prior to initial examination of the application, please amend the above-identified application as follows:

IN THE SPECIFICATION:

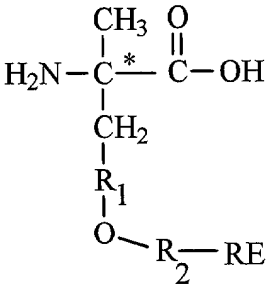
Page 1, paragraph 3, please amend as follows:

[0003] Generally speaking, PET uses radio-compounds labeled with the positron-emitters such as ^{18}F, ^{11}C, ^{13}N and ^{15}O, SPECT uses radio compounds labeled with the single-photon-emitters such as ^{18}F, ^{11}C, ^{13}N and ^{15}O, although ^{75}Br and ^{124}I can

also be used. SPECT, on the other hand, generally uses radionuclides that have more neutrons than protons, such as ^{67}Ga, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl.

Page 3, paragraph 10, please amend as follows:

[0010] The present invention includes compounds of formula (I), or pharmaceutically acceptable salts thereof:

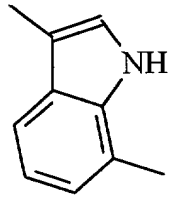


(I)

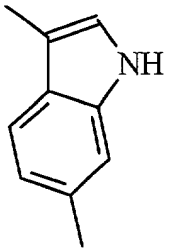
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

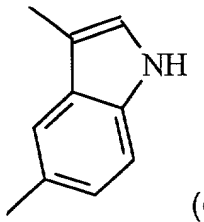
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



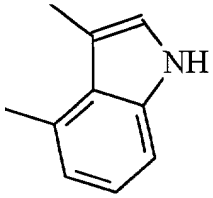
(a),



(b),



(c),



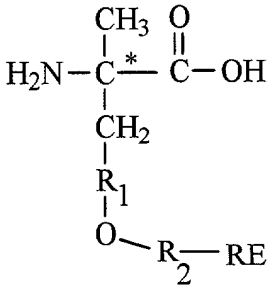
(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{67}Ga, ^{75}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl, preferably ^{123}I, ^{125}I and ^{18}F.

Page 5, paragraph 15, please amend as follows:

[0015] In this invention, compounds of formula I have been developed:

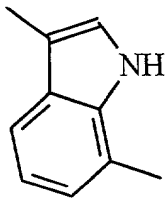


(I)

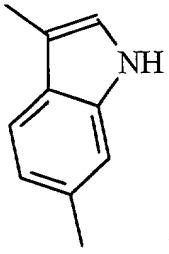
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

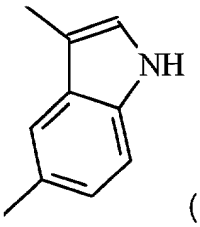
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



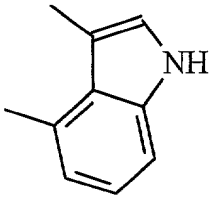
(a),



(b),



(c),



(d);

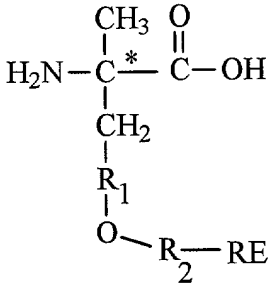
R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{67}Ga, ^{75}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl, preferably ^{123}I, ^{125}I, and ^{18}F.

IN THE CLAIMS:

Please amend the claims as follows:

1. (Once Amended) A compound of formula (I), or a pharmaceutically acceptable salt thereof:

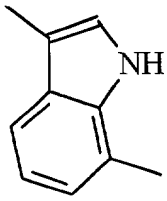


(I)

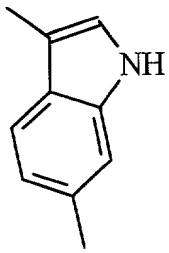
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

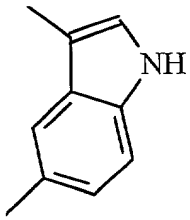
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



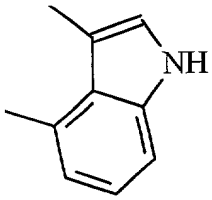
(a),



(b),



(c),

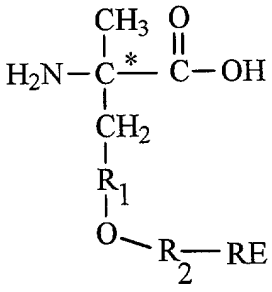


(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{123}I, ^{125}I and ^{18}F.

34. (Once Amended) A method of synthesizing a compound of formula (I):

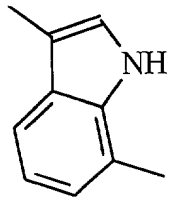


(I)

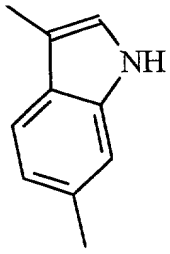
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

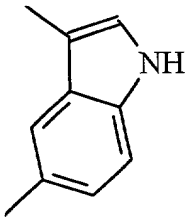
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



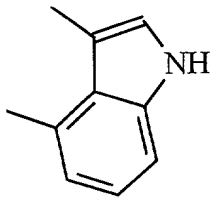
(a),



(b),



(c),



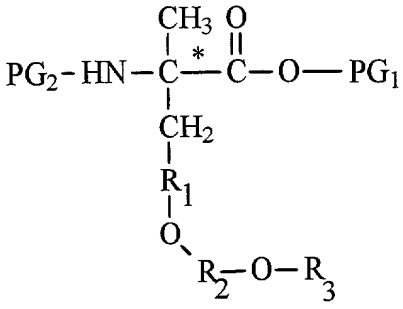
(d);

R_2 is C_1-C_7 alkyl, and

RE is selected from the group consisting of ^{123}I, ^{125}I and ^{18}F,

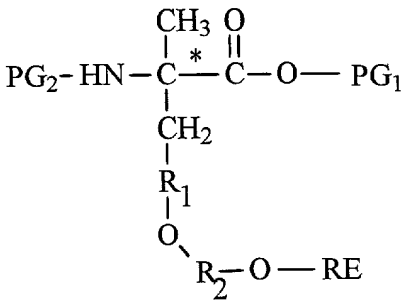
the process comprising the following steps:

(1) reacting a compound of formula (IIc):



(IIc)

wherein R_1 and R_2 are the same as above, R_3 is a leaving group, PG_1 is a carboxyl protecting group and PG_2 is an amino protecting group,
with a salt of RE, wherein RE is the same as above, to produce a compound of formula (Ia):



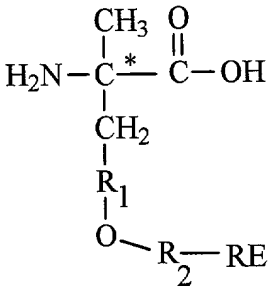
(Ia)

wherein R_1, R_2, RE, PG_1 and PG_2 are the same as above; and

(2) removing the protecting groups.

38. A method of imaging a tumor in a patient using positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging, the method comprising

administering to the patient a tumor imaging effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

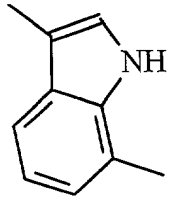


(I)

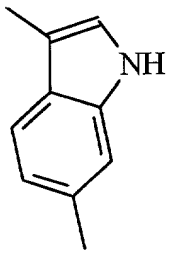
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture,

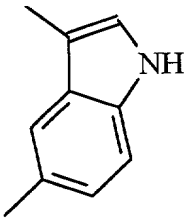
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



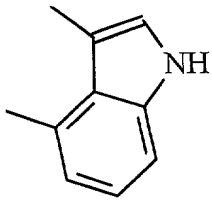
(a),



(b),



(c),



(d),

R_2 is C_1-C_7 alkyl, and

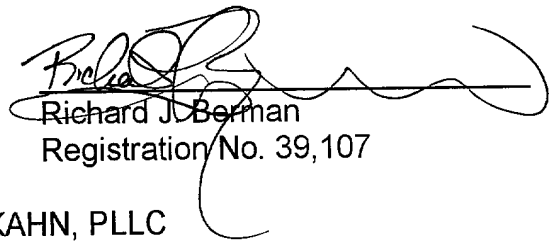
RE is selected from the group consisting of ^{123}I, ^{125}I and ^{18}F; and

imaging the tumor using PET or SPECT imaging.

REMARKS

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



Richard J. Berman
Registration No. 39,107

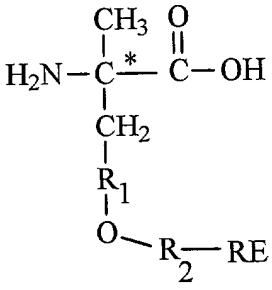
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.,
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

RJB/ccd

MARKED UP COPY OF SPECIFICATION

[0003] Generally speaking, PET uses Radio-compounds labeled with the positron-emitters such as ^{18}F, ^{11}C, ^{13}N and ^{15}O, SPECT uses radio compounds labeled with the single-photon-emitters [radionuclides that have fewer neutrons than protons, such as ^{18}F, ^{11}C, ^{13}N and ^{15}O, although ^{75}Br and ^{124}I can also be used. SPECT, on the other hand, generally uses radionuclides that have more neutrons than protons,] such as ^{67}Ga, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl.

[0010] The present invention includes compounds of formula (I), or pharmaceutically acceptable salts thereof:

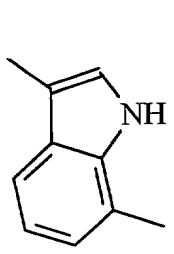


(I)

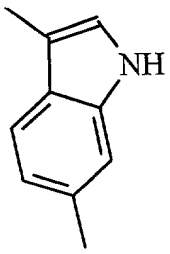
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

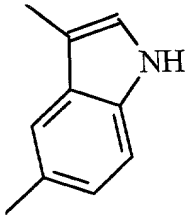
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



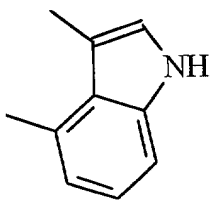
(a),



(b),



(c),

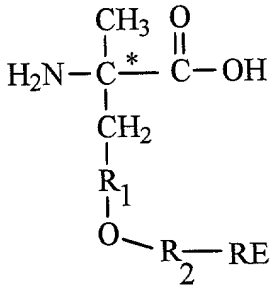


(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{67}Ga, ^{75}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl, preferably [^{75}Br, ^{124}I] ^{123}I, ^{125}I [or] and ^{18}F.

[0015] In this invention, compounds of formula I have been developed:

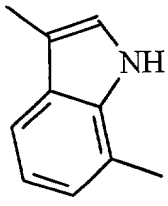


(I)

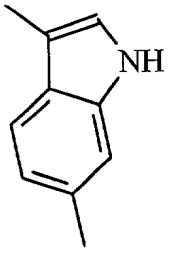
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

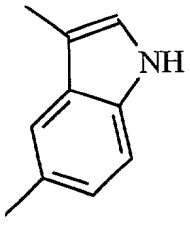
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



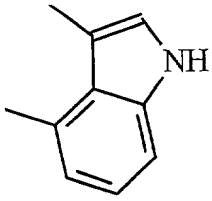
(a),



(b),



(c),



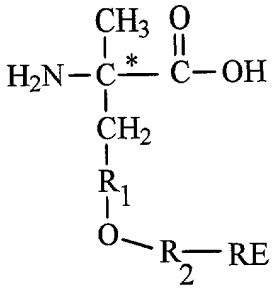
(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{67}Ga, ^{75}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{131}I and ^{201}Tl, preferably [^{75}Br, ^{124}I] ^{123}I, ^{125}I [or] and ^{18}F.

MARKED UP COPY OF CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

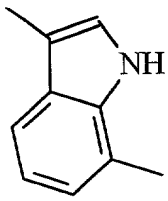


(I)

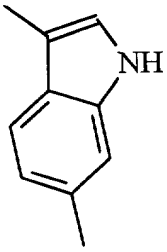
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

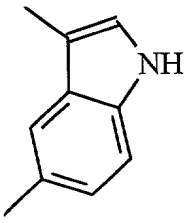
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



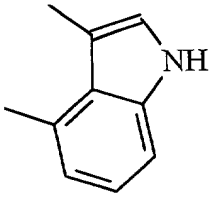
(a),



(b),



(c),

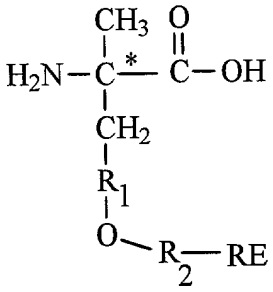


(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of [^{75}Br, ^{124}I] ^{123}I, ^{125}I and ^{18}F.

34. A method of synthesizing a compound of formula (I):

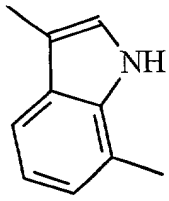


(I)

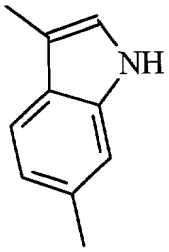
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

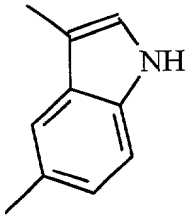
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



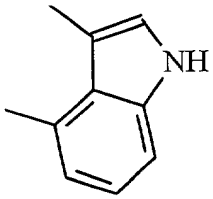
(a),



(b),



(c),



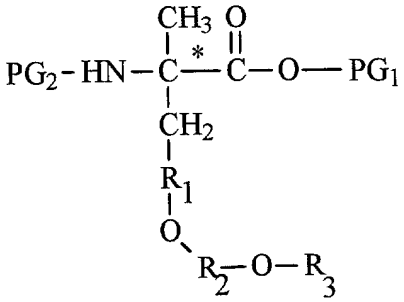
(d);

R_2 is C_1-C_7 alkyl, and

RE is selected from the group consisting of [^{75}Br, ^{124}I] ^{123}I, ^{125}I and ^{18}F,

the process comprising the following steps:

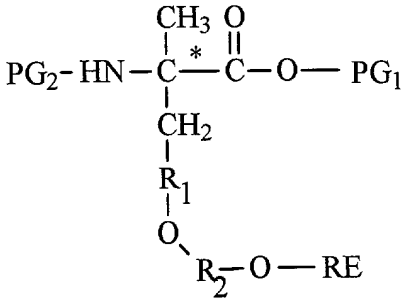
(1) reacting a compound of formula (IIc):



(IIc)

wherein R_1 and R_2 are the same as above, R_3 is a leaving group, PG_1 is a carboxyl protecting group and PG_2 is an amino protecting group,

with a salt of RE, wherein RE is the same as above, to produce a compound of formula (Ia):



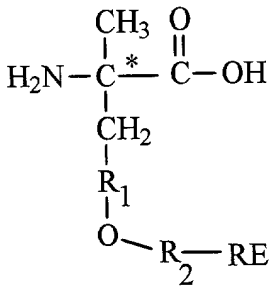
(Ia)

wherein R_1, R_2, RE, PG_1 and PG_2 are the same as above; and

(2) removing the protecting groups.

38. A method of imaging a tumor in a patient using positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging, the method comprising

administering to the patient a tumor imaging effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

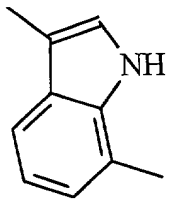


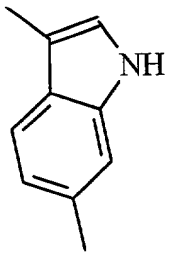
(I)

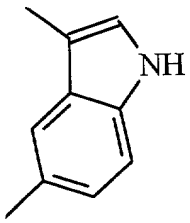
wherein

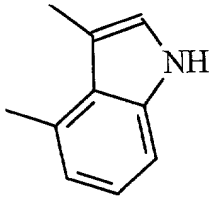
the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture,

R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



(a),


(b),


(c),


(d),

R_2 is C_1-C_7 alkyl, and

RE is selected from the group consisting of [^{75}Br, ^{124}I] ^{123}I, ^{125}I and ^{18}F; and imaging the tumor using PET or SPECT imaging.